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10/562,953	12/30/2005	Stefan G. Pierzynowski	CU-4618 BWH	8692

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EXAMINER	
BLAKELY III, NELSON CLARENCE	
ART UNIT	PAPER NUMBER
1614	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/562,953	PIERZYNOWSKI ET AL.	
	Examiner	Art Unit	
	NELSON C. BLAKELY III	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 October 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *7-39* is/are pending in the application.

4a) Of the above claim(s) *7-28* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *29-39* is/are rejected.

7)☒ Claim(s) *29,31,32,36,39 and 46* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *30 December 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *05/16/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Application Status

Claims 7-39 of the instant application are pending. Claims 1-6 are canceled, and claims 7-28 are withdrawn pursuant to Applicant's Amendment, filed 10/31/2008. Accordingly, instant claims 29-39 are presented for examination on their merits.

Election/Restrictions

Applicant's election ***with traverse*** of a method for treating malnutrition in a vertebrate, in the reply filed on 10/31/2008, is acknowledged. The traversal is on the ground(s) that the claimed species, alpha-ketoglutaric acid (AKG) derivates, metabolites, analogues, or mixtures thereof, share a technical relationship through the same biological effect and also through sharing a common partial structure. This is not found persuasive because, with regard to the examples, i.e., α-ketoglutaric acid (AKG) and chitosan-AKG, noted in the restriction/election of species requirement, mailed 10/06/2008, chitosan comprises a linear polysaccharide comprising distributed β-(1-4)-linked D-glucosamine and N-acetyl-D-glucosamine. Thus, in view of its distinct functionality, it would have been reasonable to expect its effect on the receptors and absorption rates in the gut would be different.

Additionally, in response to the restriction/election of species requirement, Applicant elected the species AKG.

Accordingly, because of reasons stated on pages 5 and 6 of the restriction/election of species requirement, mailed 10/06/2008, the requirement is still deemed proper and is therefore made **FINAL**.

Claims 7-28 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to nonelected subject matter, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 10/31/2008.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Priority

Receipt is acknowledged of the certified copy of Swedish priority application no. 0301947-8 submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file.

Information Disclosure Statement

The Information Disclosure Statement, filed 05/16/2006, is acknowledged and considered.

Specification

Applicant is reminded of the proper language and format for an abstract of the disclosure.

The Abstract should be in narrative form and generally limited to a single paragraph on a separate sheet within the range of 50 to 150 words. It is important that the abstract not exceed 150 words in length since the space provided for the abstract on the computer tape used by the printer is limited. The form and legal phraseology often used in patent claims, such as "means" and "said," should be avoided. The abstract should describe the disclosure sufficiently to assist readers in deciding whether there is a need for consulting the full patent text for details.

The language should be clear and concise and should not repeat information given in the title. It should avoid using phrases which can be implied, such as, "The disclosure concerns," "The disclosure defined by this invention," "The disclosure describes," etc.

Correction is required. See MPEP § 608.01(b).

The disclosure is objected to for the following informalities:

On page 6, line 9, for example, the recitation "ornitine" should be replaced with "ornithine".

On page 11, line 29, the recitation "vertebrate" is misspelled as "vertebratee".

The use of the trademark PLURONIC® F68 has been noted in this application, on page 14, line 2, for example. A trademark should be capitalized wherever it appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

Appropriate correction is required.

Claim Objections

Claims 29, 31, 32, 34-36 and 39 are objected to for the following informalities:

With regard to claim 29, Applicant is encouraged to insert a ", (comma)" after the recitations "...administering to the vertebrate...", in line 2, and "...effect on malnutrition...", in line 3, for the accuracy and precision of the claim language. Additionally, Applicant is encouraged to include the actual chemical name, i.e., alpha-ketoglutaric acid, before at least at the first occurrence of the term "AKG" for the accuracy and precision of the claim language.

With regard to claim 31, the recitation "ornithine" is misspelled as "ornitine".

With regard to claims 32 and 34-36, Applicant is encouraged to insert a ", (comma)" after the claim number, i.e., "The method according to claim 29,...".

With regard to claim 39, Applicant is encouraged to use proper Markush language format, i.e., "...wherein the essential amino acid is selected from a group consisting of isoleucine...".

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 29, 30, 31 (in part) and 32-39 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. It is noted that Applicant sets forth the derivates contemplated in instant claim 31; however, with regard to the amino acid derivates, in line 5, the rejection is set forth *infra*.

The instant claims recite the limitation AKG (alpha-ketoglutaric acid) derivates, metabolites and analogues, or mixtures thereof, and amino acid derivates. Applicant has not described the claimed genus of derivates, metabolites, analogues and amino acid derivates in a manner that would indicate Applicant was in possession of the full scope of this genus, or describe of what this genus is comprised. The instant specification, on page 8, lines 10-15, discloses wherein the term "derivative", or "derivate", is intended to mean a chemical substance derived from a mother substance either directly or by modification or partial substitution. Additionally, in the instant excerpt, the instant specification discloses wherein the term "analogue", for example, is intended to mean compounds that are structurally similar to another, but are not necessarily isomers. These exemplifications are not definitions that allow the Examiner,

or one of ordinary skill in the art, to ascertain that Applicant was in possession of the full scope of this genus.

Regarding the requirement for adequate written description of chemical entities, Applicant's attention is directed to the MPEP § 2163. In particular, *Regents of the University of California v. Eli Lilly & Co.*, 119 F.3d 1559, 1568 (Fed. Cir. 1997), cert. denied, 523 U.S. 1089, 118 S. Ct. 1548 (1998), holds that an adequate written description requires a precise definition, such as by structure, formula, chemical name, or physical properties, "not a mere wish or plan for obtaining the claimed chemical invention." *Eli Lilly*, 119 F.3d at 1566. The Federal Circuit has adopted the standard set forth in the Patent and Trademark Office ("PTO") Guidelines for Examination of Patent Applications under the 35 U.S.C. 112.1 "Written Description" Requirement ("Guidelines"), 66 Fed. Reg. 1099 (Jan. 5, 2001), which state that the written description requirement can be met by "showing that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics, "including, *inter alia*, "functional characteristics when coupled with a known or disclosed correlation between function and structure..." *Enzo Biochem, Inc. v. Gen-Probe Inc.*, 296 F.3d 316, 1324-25 (Fed. Cir. 2002) (quoting Guidelines, 66 Fed. Reg. at 1106 (emphasis added)). Moreover, although Eli Lily and Enzo were decided within the factual context of DNA sequences, this does not preclude extending the reasoning of those cases to chemical structures in general. *Univ. of Rochester v. G.D. Searle & Co.*, 249 Supp. 2d 216, 225 (W.D.N.Y. 2003).

In the instant case, Applicants have not described the genus of AKG derivates, metabolites, analogues and amino acid derivates in a manner that would allow one skilled in the art, at the time of the invention, to immediately envisage the compounds contemplated for use. As such, the claims lack adequate written description for the claimed AKG derivates, metabolites, analogues and amino acid derivates.

Claims 29-39 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for alleviating or treating malnutrition in a vertebrate, does not reasonably provide enablement for a method for preventing malnutrition in a vertebrate. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

As stated in the MPEP § 2164.01(a), "There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue."

In *In re Wands*, 8 USPQ2d 1400 (1988), factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have need described. They are:

1. The nature of the invention
2. The state of the prior art
3. The predictability or lack thereof in the art
4. The amount of direction or guidance present
5. The presence or absence of working examples
6. The breadth of the claims

7. The quantity of experimentation needed, and
8. The level of skill in the art

It is noted that all of the Wands factors have been considered with regard to the instant claims, with the most relevant factors discussed below.

The Predictability or lack thereof in the art

It is noted that the Applicant states where the present invention provides new and improved methods for preventing, treating and/or alleviating diabetes and malnutrition, on page 5, lines 34-39 of the instant specification; however, the generally accepted definition of "prevent", which is commensurate in scope with Applicant's definition on page 8, lines 21-24, is to keep from occurring, or to anticipate. Therefore, by the Examiner's broadest reasonable interpretation of the claims to Applicant's method for preventing malnutrition in a vertebrate (instant claim 29; in part), the "prevention" of malnutrition lacks enablement. Undue experimentation would be required to predictably practice the prevention embodiments by Applicant's instant disclosure. Thus, since the instant specification does not provide sufficient guidance as to how the pharmaceutical composition comprising at least α-ketoglutaric acid could be used to prevent malnutrition, it would require undue experimentation to practice the invention as broadly claimed. Additionally, the disclosure is silent with regard to that which makes up and identifies the claimed method for preventing malnutrition, which is seen to be lacking a clear description via art recognized procedural and methodological steps.

The Amount of Direction or Guidance Present and Presence or Absence of Working Examples

The only direction or guidance present in the instant specification is with regard to the treatment of malnutrition, on page 12, lines 34-36, for example. There is no data present in the specification for the "prevention" of malnutrition. The specification only discloses on page 5, lines 34-39, for example, that the method may be used for prevention, treatment and/or alleviation of malnutrition. The guidance in the specification is limited to the disclosure that the composition treats malnutrition; however, it is not discussed such that one skilled in the art is provided sufficient guidance to practice a method of prevention.

The Breadth of the Claims

The instant breadth of the rejected claims is broader than the disclosure; specifically, the instant claims include "prevention" of *any* form of malnutrition.

The Quantity of Experimentation Needed and the Level of Skill in the Art

While the level of skill in the pharmaceutical arts is high, it would require undue experimentation for one of ordinary skill in the pertinent art to prevent *any* form of malnutrition. The science of drug development has evolved such that, without guidance or working examples in the specification, the claims lack enablement.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 31, 35 and 39 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

With regard to claim 31, the phrase "such as" renders the claim indefinite because it is unclear whether or not the limitation following the phrase is part of the claimed invention. See MPEP § 2173.05(d).

With regard to claim 35, the recitation "a free going farm animal" renders the claim indefinite. The recitation is not defined by the claim, and the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art, at the time of the invention, would not be reasonably apprised as to the scope of the invention.

With regard to claim 39, the term "and" renders the claim indefinite. Confusingly, it is unclear to the Examiner, or one of ordinary skill in the art, at the time of the invention, whether or not all of the instantly claimed essential amino acids are required, a combination, or only one amino acid. It is noted that the recitation "essential amino acid" is singular; therefore, for the purposes of the initial examination, the Examiner will interpret the claim whereby the Applicant intended to use proper Markush claim language, and whereby only one of the listed essential amino acids is required. Applicant is encouraged to amend the claim to clarify this confusion.

Claim Rejections - 35 USC § 102

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 29-32 and 37-39 are rejected under 35 U.S.C. 102(b) as being anticipated by Riedel *et al.* (Nephron, Vol. 74, No. 2, pages 261-265; 1996; Cited by Applicant).

With regard to instant claims 29-32 and 37-39, Riedel *et al.* disclose, in the Abstract, wherein the free amino acids and α-ketoacids in plasma were determined by fluorescence HPLC to assess the effect of α-ketoglutarate administration in combination with the phosphate binder calcium carbonate on the amino acid metabolism. In the instant excerpt, Riedel *et al.* further disclose during one year of therapy in parallel to inorganic phosphate, urea in plasma decreased significantly, and amino acids, i.e., proline, increased. Furthermore, Riedel *et al.* concluded that the administration of α-ketoglutarate with calcium carbonate effectively improves amino acid metabolism in hemodialysis patients. In the last paragraph of the Introduction, Riedel *et al.* disclose wherein the aim of the study was to clarify whether or not the reference medication, in phosphate-binding doses in hemodialysis patients, is able to improve amino acid metabolism and malnutrition. In Figures 1 and 2, and column two, last paragraph, on page 263, Riedel *et al.* disclose where amino acids, such as leucine and lysine, showed significantly increased plasma concentrations. Additionally, Riedel *et al.* disclose, on page 264, column two, lines 14-20 of text, wherein the significant increase of plasma concentrations of proline, for example, is due to the consequence of increased production of glutamate via transamination of the supplemented α-ketoglutarate.

Accordingly, instant claims 29-32 and 37-39 are anticipated by Riedel *et al.*, and properly rejected under 35 U.S.C. 102(b).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 29-39 are rejected under 35 U.S.C. 103(a) as being unpatentable over Riedel *et al.* (Nephron, Vol. 74, No. 2, pages 261-265; 1996; Cited by Applicant), as applied to claims 29-32 and 37-39 above, and further in view of Plouvier *et al.* (US

Patent Application Publication No. 2004/0127413A1) and Shiflett *et al.* (Journal of Nutrition, Vol. 98, pages 420-426; 1969).

With regard to instant claims 29-32 and 37-39, the teachings of Riedel *et al.* have been set forth *supra*.

With regard to instant claims 33-36, Riedel *et al.* fail to disclose specifically wherein the vertebrate is a rodent, i.e., a rat, a bird, i.e., a chicken, a farm animal, i.e., a cow, or a domestic pet, i.e., a dog. However, Plouvier *et al.* disclose in reference claims 1-3, 5-9, 33, 35 and 42, a method of treating a mammal in need of treatment, comprising administering a therapeutically effective amount of the enteric composition comprising at least one compound of the empirical formula (I) to the mammal, i.e., human being, suffering from malnourishment. In the instant excerpt, Plouvier *et al.* further disclose wherein the empirical formula (I), i.e., $(X)n_1Y(X)n_2$, comprises wherein X is ornithine, lysine, arginine, proline or glutamine, wherein n_1 is 1 and n_2 is 0, and wherein Y is alpha-ketoglutaric acid.

Plouvier *et al.* fail to disclose specifically wherein the mammal is a vertebrate mentioned *supra*; however, one of ordinary skill in the art, at the time of the invention would have construed the term "mammal", which is a class of vertebrate animals whose name is derived from their distinctive feature, mammary glands, to encompass a rat, a cow or a dog, for example. Plouvier *et al.* fail to disclose specifically wherein vertebrate is a bird, i.e., chicken; however, Shiflett *et al.* disclose, in the Abstract, a study to test the effect of vitamin B_6 deficiency on levels of leucine transaminase activity in various tissues of chicks. In the instant excerpt, Shiflett *et al.* further disclose that after 8 days,

chicks fed a deficient diet, comprising zero or 1.2 mg pyridoxine·HCl/100 g, showed evidence of severe vitamin B_6 deficiency, which resulted in anorexia and retarded growth, for example. Furthermore, Shiflett *et al.* disclose where leucine transaminase activity was significantly decreased in the kidney of chicks fed the deficient diet for 1.5 days. Additionally, Shiflett *et al.* disclose, on page 420, column 1, line 1-10, wherein the purpose of the study was to investigate the unreported effect of vitamin B_6 deficiency on the activity of the leucine transaminases, which catalyze the transamination of the branched-chain amino acids essential for animals, with alpha-ketoglutaric acid.

Therefore, a skilled artisan, at the time of the invention, would have envisaged the method of treating malnutrition in a vertebrate, comprising administering a composition comprising α-ketoglutaric acid and an amino acid, i.e., ornithine, as disclosed by Riedel *et al.*, in view of Plouvier *et al.* One of ordinary skill in the art would have been motivated to combine the teachings of the aforementioned references when seeking a therapeutically effect medicament, with doses low enough to avoid unwanted side effects, in the treatment of a malnourished vertebrate. A skilled artisan, at the time of the invention, would have also been motivated to use the methods, wherein the vertebrate is a chicken, for example, as disclosed by Shiflett *et al.*, when contemplating the treatment of malnutrition, i.e., anorexia, in an animal destined for use in food production, for example. It would have been obvious to one of ordinary skill in the art, at the time of the invention, because the combined teachings of the prior art are fairly suggestive of the claimed invention.

Accordingly, the instant invention, as claimed in claims 29-39, is *prima facie* obvious over the combination of the aforementioned teachings.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to NELSON C. BLAKELY III whose telephone number is (571) 270-3290. The examiner can normally be reached on Mon - Thurs, 7:00 am - 5:30 pm (EST).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin H. Marschel can be reached on (571) 272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Phyllis G. Spivack/
Primary Examiner, Art Unit 1614
January 15, 2009

/N. C. B. III/
Examiner, Art Unit 1614